Mismatch negativity encoding of prediction errors predicts ketamine-induced thought disorders

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Background

Pharmacological challenges with N-methyl-D-aspartate receptor (NMDAR) antagonists and 5-hydroxytryptamine2A receptor (5-HT_2A) agonists have been used to produce psychosis-like symptoms in healthy humans [1]. Although NMDA antagonists have been repeatedly and faithfully reproduced the full spectrum of psychopathology associated with schizophrenia than 5-HT_2A agonists, both classes of drugs engender a number of positive symptoms in common that are similar to those observed in schizophrenia. However, a neurocognitive underpinning the formation of positive-like symptoms and particularly of thought disorder in these two models of psychosis is still missing. Recent theories of psychosis posit that aberrant encoding of prediction errors (PE) may lead to positive-like symptoms [2]. This study investigated whether the encoding of PE depicted via the mismatch negativity (MMN) event-related potential (ERP) depends on NMDA and/or 5-HT_2A neurotransmission, and whether the effects of ketamine and psilocybin administration on MMN can be used to predict thought disorders in healthy volunteers.

Methods

Two groups (ketamine: N = 19; psilocybin: N = 20) of healthy subjects received in a double-blind, within-subjects design placebo versus ketamine or psilocybin. Ketamine infusion was initiated with a 10 mg bolus over 5 min, followed by a continuous infusion with 0.006mg/kg/min. Psilocybin was given p.o. at a dose of 115 μg/kg. The MMN memory trace effect (MMN slope) was measured using a roving oddball design [3] (Figure 1). Note that the MMN slope response is due to learning and cannot be due to differential states of frequency-specific auditory neurons in the temporal cortex. ERP recordings were made from 64 scalp electrodes (10–20 system). A set of fronto-central (Fz, F3 and F4) and temporal electrodes (TP7 and TP8) were selected for statistical analysis. At the end of each ERP recording session, psychosis-like symptoms were assessed using a modified Altered States of Consciousness Rating Scale, with focus on positive-like symptoms.

Results

As predicted, the MMN response under placebo increased systematically with number of standard repetitions at frontal electrodes (F2, F3 and F4) following placebo (green) or drug administration (red: ketamine; blue: psilocybin), respectively. This memory trace effect (MMN slope) was significantly disrupted by ketamine but not by psilocybin as evidenced by a significant triple interaction between electrode, treatment, and standard repetition ([F(1,37) = 8.4, p < .005, η^2 = .19], but not by psilocybin (Figure 2).

Although both drugs produced positive-like symptoms (Figure 3), the extent of PE over placebo only correlated significantly with the severity of cognitive impairments induced by S-ketamine (r = −.67; p < .005). In the psilocybin group, no comparable correlations were found.

Conclusion

The present results suggest that the frontal MMN memory trace effect may provide a useful approach to study NMDAR-dependent PE processing during the MMN as a form of implicit perceptual learning. Unraveling the role of NMDAR function in predictive coding may provide valuable insights into pathophysiological mechanisms of schizophrenia in general and the emergence of cognitive impairments in psychosis in particular. This may particularly benefit from a computational modeling approach using physiologically interpretable model parameters for clinical predictions (Stephan et al, 2006). In relation to this, recent studies demonstrated that a reduction of MMN can predict the transition of “ultra-high risk” to first-episode psychosis (Bodach et al, 2010; Shin et al, 2009). Finally, the assessment of the MMN memory trace effect may also provide a promising tool to assess the efficacy of novel pharmacological treatment, in particular for treatment of cognitive impairments.

Disclosure

The authors declare no conflict of interests.

References